2H

# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/849,603 | 05/18/2004 | Andrew Simon Craig | P32672C1 | 7390 |

7590 03/21/2005

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

| EXAMINER | |
|---|---|
| MORRIS, PATRICIA L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1625 | |

DATE MAILED: 03/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 10/849,603 | Applicant(s) CRAIG ET AL. | |
|---|---|---|---|
| | Examiner Patricia L. Morris | Art Unit 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/381,496.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-9 are under consideration in this application.

Claims 10-12 are held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

### *Election/Restrictions*

Applicant's election with traverse of Group I in the reply filed on February 4, 2005 is acknowledged. The traversal is on the ground(s) that there is no undue burden on the examiner to search all the inventions. This is not found persuasive because for the reasons clearly set forth in the previous Office action. Further, applicants have failed to advance any cogent reasons as to why the inventions are not patentably distinct. Group III will not be rejoined with Group I because it differs in scope in scope from Group I. Group II will not be rejoined because the compound of Group I is not allowable because it is a well known prior art compound. Note the prior art of record.

The requirement is still deemed proper and is therefore maintained.

### *Specification*

The specification fails to give a Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74. Correction is required.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 are rejected under 35 U.S.C. 102(a) and/or (e) as being anticipated by Fischer et al. (WO 01/44240) and Song et al. (CN 1253136A).

Fischer et al. and Song et al. teach the instant salt. Note example 3 of Fischer et al. and claims 1 and 3 of Song et al. Hence, the instant salt is deemed to be anticipated therefrom.

*Claim Rejections - 35 USC ∋ 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Fischer et al. and Song et al. in view of Haleblian et al. J of Pharmaceutical Sciences, (1969), 58, pp 911-929, Chemical & Engineering News, Feb. 2003, US Pharmacopia, 1995, pp 1843-1844, Brittain et al. (Polymorphism in Pharmaceutical Solids, NY: Marcel Dekker, Inc., 1999, pages 125-181, 183-226, 228-330 +331-361) and Concise Encyclopedia Chemistry, page 872-873 (1993).

Fischer et al. and Song et al. teach the cystal forms of the instant known compound and as well as the pharmaceutical compositions. Note example 3 of Fischer et al. or claims 1 and 3 of Song et al.. Haleblian et al. and Brittain et al. teach that compounds exist as polymorphs. Chemical & Engineering News, US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

### *Claim Rejections - 35 USC ∋ 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The expression solvate is employed in claims 1 and 5 with no indication given as to what the solvates really are. The references of record show that solvents can affect chemical stability of the compounds. For example, note column 2 on page 913 of Haleblian et al or page 199 of Brittain et al.

One should be able, from a reading of the claims, determine what that claim does or does not encompass.

Why? Because that claim precludes others from making, using, or selling that compound for 20 years. Therefore, one must know what compound is being claimed.

The unknown solvates are so broad that they cause the claim to have a potential scope of protection beyond that which is justified by the specification disclosure.

The written description is considered inadequate here in the specification. Conception of the intended solvates should not be the role of the reader. Applicants should, in return for a 20 year monopoly, be disclosing to the public that which they know as an actual demonstrated fact. The disclosure should not be merely an invitation to experiment. This is a 35 USC 112, first paragraph. If you (the public) find that it works, I claim it, is not a proper basis of patentability. In re Kirk, 153 USPQ 48, at page 53.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that the instant compounds are made prepared according to methods disclosed in EP 306,228 and WO 94/05659. However, different polymorphic forms of the salts of the compound of claim 1 have also been disclosed as being made by the same methods as described in EP 306,228 and WO 94/05659. However, different polymorphs cannot be produced by the same method. It is impossible to synthesize more than one metastable polymorphic form using the same method to synthesize the different forms. At a given temperature and pressure, only one polymorph can be produced. Note, for example, page 873 of Concise Encyclopedia Chemistry. There is also a lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form or solvates claimed. Desolvation may occur. Note page 290 of Brittain. Processing a compound into a pharmaceutical composition could desolvate or create a different polymorph than the polymorphs being claims or even back to the compound itself. See pages 912-913 of Habeblian.

The specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. The X-ray diffraction and Infrared spectrum data in the specification only pertains to the compounds rather than the compositions being claimed.

There is also no description as to how applicants produced and isolated the particular solvates being claimed. Only when solvent is incorporated into the crystal lattice of the compound in stoichiometric proportions, are particular solvates formed. (See page 281 of

Brittain or page 143 of U.S. Pharmacopia). Applicants would have to show how the particular solvates are isolated.

Chemical & Engineering News discloses that formulation of drugs or pharmaceuticals in its metastable forms, for example, one polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. The specification lacks description of how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Disclosure of X-ray diffraction patterns for pharmaceutical compositions comprising the polymorphic forms are lacking in the specification. The X-ray diffraction patterns and infrared spectra on pages 8-9 and the referenced figure 1 only supports the polymorphic forms of the compounds and not the pharmaceutical compositions. The specification has also not described how the polymorph forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment or prevention of diabetes mellitus.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor,

7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

***The nature of the invention***

The nature of the invention is the preparation of novel polymorphic forms of the instant salt and solvates thereof and compositions.

***State of the Prior Art***

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Additionally, solids may form solvates. Polymorphs tend to convert from less stable to more stable forms. (See Chemical Engineering News, page 32). No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best work with the most stable polymorph, because it will not covert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News. Page 33, which will changed the pharmacological affects of the drug. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

*The amount of direction or guidance and the presence or absence of working examples*

Figures 1-4 and pages 10-11 of the specification only disclose the X-ray diffraction pattern and infrared spectra of compounds of particular forms rather than the compositions being claimed in terms of the specific X-ray diffraction patterns. Polymorphs often change into other polymorphs during drug manufacture (See Chemical Engineering News) into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the pharmaceutical compositions.

Further, the specification fails to show that the instant polymorphs treat or prevent diabetes mellitus. As evidenced by the art of record, it is well known that polymorphs can convert to the original compound.

*The breadth of the claims*

The breadth of the claims are drawn to the specific polymorph form and all unknown solvates in addition to the pharmaceutical compositions.

*The quantity of experimentation needed*

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification. There is also lack of guidance as to whether the instant polymorph rather than the original compound treats or prevents diabetes mellitus.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of

unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term solvate in claims 1 and 5 is indefinite to its meaning.

Claims 2-4 lack antecedent basis for the recited limitations. All the claims are drawn to the compound of claim 1.

The expression "substantially in accordance" in claim 2 is indefinite to its meaning. There is insufficient antecedent basis for the limitations.

Claim 2 is incomplete because the claims are not self-contained in particularly pointing out and distinctly claiming what applicants regard as their invention. This practice facilitates examination of the claimed invention by having the subject matter all in one place, avoids complicating the examination process by adding the processing of drawings and possible correction thereof, and permits the claimed subject matter to be easily modified without possible correction of drawings and potential modification of the scope of the disclosure as originally filed. Further, the public should not have to refer to the claimed subject matter in one place and not have to refer back and forth to at least two or three different places.

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The U.S. Court of Claims held to this standard in Lockheed Aircraft Corp. v. United States, 193 USPQ 449, AClaims measure invention and resolution of invention must be based on what is claimed≅.

The C.C.P.A. in 1978 held a that invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim≅: In re Priest, 199 USPQ 11, at 15.

### *Drawings*

The formal drawings filed on May 18, 2004 have been accepted.

### *Priority*

Applicants are requested to update the status of the parent application, Ser. No. 10/381,496, on page 1, line 1 of the specification. Cooperation herein is appreciated.

### *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patricia L. Morris
Primary Examiner
Art Unit 1625

plm
March 10, 2005